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10/730,549	12/05/2003	Mary J. Laughlin	CWRU-P01-046	1488

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EXAMINER	
BARNHART, LORA ELIZABETH	
ART UNIT	**PAPER NUMBER**
1651	

DATE MAILED: 11/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/730,549	LAUGHLIN ET AL.	
	Examiner	Art Unit	
	Lora E. Barnhart	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-57,62 and 63* is/are pending in the application.

4a) Of the above claim(s) *5,9,18,22,37-39 and 48* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6-8,10-17,19-21,23-36,40-47,49-57,62 and 63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/3/04, 12/1/05, 4/26/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendments

Applicant's amendments filed 10/4/06 to claims 2, 3, 7-10, 15, 16, 21, 22, 24, 26-28, 30, 36, 43, 50, 54, and 57 have been entered. Claims 58-61 have been cancelled. Claims 62 and 63 have been added. Claims 1-57, 62, and 63 remain pending in the current application.

Election/Restrictions

Applicant's election with traverse of Group I, claims 1-57, in the reply filed on 10/4/06 is acknowledged. The traversal is on the ground(s) that examining both Groups would not be burdensome to the examiner. This is not found persuasive because burden consists not only of specific searching of classes and subclasses, but also of searching multiple databases for foreign references and literature searches. Burden also resides in the examination of independent claim sets for clarity, enablement and double patenting issues. It is also noted for the record that applicant has canceled all claims in Group II.

The requirement is still deemed proper and is therefore made FINAL.

Applicant's election of various species, including "allogeneic" for the relationship of the endothelial progenitor cells to the subject; "hemangioblasts" as the endothelial progenitor cells; "bone marrow" as the source of mesenchymal stem cells; "autologous" for the relationship of the mesenchymal stem cells to the subject; "myocardial ischemia" as the disorder; "not modified by the introduction of exogenous DNA" as the genetic state of the endothelial generating cells; and "VEGF" as the polypeptide coadministered

with the cells, in the reply filed on 10/4/06 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Claims 5, 9, 18, 22, 37-39, and 48 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 10/4/06.

Examination on the merits will commence at this time on claims 1-4, 6-8, 10-17, 19-21, 23-36, 40-47, 49-57, 62, and 63 ONLY, to the extent they read on the elected species where applicable.

Claim Objections

Claim 12 is objected to because of the following informalities: A space should be inserted before the word "VE-cadherin" at line 2. Appropriate correction is required.

Claim 63 is objected to because of the following informalities: The claim should read "are administered" at line 2. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3, 8, and 16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 3 recites the limitation "the endothelial progenitor cells" in line 1. There is insufficient antecedent basis for this limitation in the claim. Claim 1 does not recite endothelial progenitor cells. Clarification is required.

Claim 8 requires expanding endothelial generating cells (EGCs) under "endothelial cell-promoting culture conditions," but these conditions are not particularly pointed out in the claim. Clarification is required.

Claim 16 appears to be identical in scope to claim 2. Clarification is required. One of these claims should be canceled. Similarly, applicant's attention is drawn to claims 3 and 15, which are nearly identical in scope.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-4, 6-8, 11-17, 19-21, 23-28, 32-36, 40-47, and 49-57 are rejected under 35 U.S.C. 102(a) as being anticipated by Ueno et al. (2002, U.S. Patent Application Publication 2002/0037278; reference A) taken in light of Yin et al. (1997, *Blood* 90: 5002-5012; reference CWW on 12/3/04 IDS) and Haynesworth (1992, *Bone* 13: 69-80; reference U). The claims are interpreted as being drawn to a method for treating

ischemic tissue in a subject comprising administering a therapeutically effective amount of enriched human endothelial generating cells (EGCs) and enriched human mesenchymal stem cells (MSCs). In some claims, the ischemic tissue is ischemic myocardium and the EGCs are endothelial precursor cells (EPCs). In some dependent claims, the EGCs are hemangioblasts or are generated in culture from hemangioblasts. In some dependent claims, the EGCs and MSCs are isolated from bone marrow. In some dependent claims, the EGCs and MSCs are enriched and/or culture-expanded before the administration step. In some dependent claims, the EGCs and MSCs are HLA compatible with the subject and the MSCs are autologous to the subject. In some dependent claims, the EGCs and MSCs express particular markers. In some dependent claims, the amount of cells administered is particularly pointed out. In some dependent claims, the mode of administration is particularly pointed out. In some dependent claims, a recombinant polypeptide is coadministered with the cells. In some claims, the ischemic tissue is ischemic myocardium and the EGCs are endothelial precursor cells (EPCs).

Ueno et al. teach isolating bone marrow (BM) from a mammal (for example, paragraphs 0057-0059), which may be a human (paragraph 0037); isolating bone marrow mononuclear cells (BM-MNCs) therefrom, thus enriching the fraction (paragraph 0059); culturing the BM-MNCs (paragraphs 0061 and 0062, for example); and administering the BM-MNCs to ischemic tissue, specifically ischemic myocardium in a subject in need thereof (paragraphs 0100-0104, for example), which is preferably a human (paragraph 0053). Ueno et al. teach that BM-MNC inherently comprises both

MSCs and EPCs (paragraph 0033) and that EPCs inherently express CD34 (paragraph 0031, for example). Ueno et al. teach administering approximately $6.9x10^6$ BM-MNCs to the subject (paragraph 0074) directly into the ischemic tissue (paragraph 0074) or, in the case of ischemic myocardium, via an injection catheter into the tissue (paragraph 0103, for example). Ueno et al. teach transfecting the BM-MNCs with a vector that produces recombinant VEGF (paragraphs 0040-0042, for example)

Yin et al. is cited as evidence that EPCs inherently express CD133, also termed AC133 (Abstract; page 5010, column 1, paragraph 3-4). Haynesworth et al. is cited as evidence that MSCs inherently express SH2, SH3, and SH4 (Abstract; Figures 1 and 2).

Claim 2 is included in this rejection because the EPCs of Ueno et al. are considered "hemangioblasts" by virtue of their ability to form both endothelial tissue (as shown by Ueno et al.) and hematopoietic cells (as indicated by their expression of the hematopoietic marker CD34). Claims 3, 15, and 20 describe components by product-by-process limitations (*e.g.* "wherein the EPCs are generated in culture from hemangioblasts") that do not materially affect the structural or physical properties of said components; see M.P.E.P. § 2113. Claim 4 recites inherent effects of the method of claim 1.

Claims 1-4, 6-8, 11-17, 19-21, 23-28, 32-36, 40-47, and 49-57 are also rejected under **35 U.S.C. 102(e)** as being anticipated by Ueno et al. taken in light of Yin et al. and Haynesworth for the reasons set forth above.

Claims 1-4, 6, 7, 11-17, 20, 21, 23-28, 32, 33, 44-46, and 50-57 are rejected under 35 U.S.C. 102(a) as being anticipated by Tateishi-Yuyama et al. (2002, *The Lancet* 360: 427-435; reference CR on 12/3/04 IDS) taken in light of Ueno et al., Haynesworth, and Yin et al. The claims are interpreted as being drawn to a method for treating ischemic tissue in a subject comprising administering a therapeutically effective amount of enriched human endothelial generating cells (EGCs) and enriched human mesenchymal stem cells (MSCs). In some claims, the EGCs are endothelial precursor cells (EPCs). In some dependent claims, the EGCs are hemangioblasts or are generated in culture from hemangioblasts. In some dependent claims, the EGCs and MSCs are isolated from bone marrow. In some dependent claims, the EGCs and MSCs are enriched before the administration step. In some dependent claims, the EGCs and MSCs are HLA compatible with the subject and the MSCs are autologous to the subject. In some dependent claims, the EGCs and MSCs express particular markers. In some dependent claims, the amount of cells administered is particularly pointed out. In some dependent claims, the mode of administration is particularly pointed out. In some claims, the ischemic tissue is ischemic myocardium and the EGCs are endothelial precursor cells (EPCs).

Tateishi-Yuyama et al. teach isolating bone marrow (BM) from a human (page 429, column 1, paragraph 2); isolating bone marrow mononuclear cells (BM-MNCs) comprising both $CD34^+$ and $CD34^-$ cells (page 431, column 1, paragraph 4) therefrom and concentrating them, thus enriching the fraction (page 429, column 2, paragraph 2); and administering over 10^9 BM-MNCs to ischemic tissue, specifically ischemic leg tissue

in a subject in need thereof (page 429, column 1, paragraph 2). Tateishi-Yuyama et al. teach that said injections resulted in increased blood flow in the treated limbs (Figures 3 and 4) and increased collateral vessel formation (Figure 5) in the treated limbs.

Ueno et al. is cited as evidence that BM-MNC inherently comprises both MSCs and EPCs (paragraph 0033) and that EPCs inherently express CD34 (paragraph 0031, for example).

Yin et al. is cited as evidence that EPCs inherently express CD133, also termed AC133 (Abstract; page 5010, column 1, paragraph 3-4). Haynesworth et al. is cited as evidence that MSCs inherently express SH2, SH3, and SH4 (Abstract; Figures 1 and 2).

Claim 2 is included in this rejection because the EPCs of Ueno et al. inherently present in the BM-MNCs of Tateishi-Yuyama et al. are considered "hemangioblasts" by virtue of their ability to form both endothelial tissue (as shown by Ueno et al.) and hematopoietic cells (as indicated by their expression of the hematopoietic marker CD34). Claims 3, 15, and 20 describe components by product-by-process limitations (*e.g.* "wherein the EPCs are generated in culture from hemangioblasts") that do not materially affect the structural or physical properties of said components; see M.P.E.P. § 2113. Claim 4 recites inherent effects of the method of claim 1.

Claims 1-4, 6-8, 11-17, 19-21, 23-28, 32-34, 36, 44-47, and 49-57 are rejected under 35 U.S.C. 102(a) as being anticipated by Strauer et al. (2002, *Circulation* 106: 1913-1918; reference CAAA on 12/3/04 IDS) taken in light of Ueno et al., Haynesworth, and Yin et al. The claims are interpreted as being drawn to a method for treating

ischemic tissue in a subject comprising administering a therapeutically effective amount of enriched human endothelial generating cells (EGCs) and enriched human mesenchymal stem cells (MSCs). In some claims, the tissue is myocardium and EGCs are endothelial precursor cells (EPCs). In some dependent claims, the EGCs are hemangioblasts or are generated in culture from hemangioblasts. In some dependent claims, the EGCs and MSCs are isolated from bone marrow. In some dependent claims, the EGCs and MSCs are enriched and/or culture-expanded before the administration step. In some dependent claims, the EGCs and MSCs are HLA compatible with the subject and the MSCs are autologous to the subject. In some dependent claims, the EGCs and MSCs express particular markers. In some dependent claims, the amount of cells administered is particularly pointed out. In some dependent claims, the mode of administration is particularly pointed out. In some claims, the ischemic tissue is ischemic myocardium and the EGCs are endothelial precursor cells (EPCs).

Strauer et al. teach isolating bone marrow (BM) from humans (page 1914, column 1, paragraph 5); isolating bone marrow mononuclear cells (BM-MNCs) therefrom, thus enriching the fraction compared to whole marrow (*ibid.*); cultivating them overnight (page 1914, column 2, paragraph 1) and administering over 10^6 BM-MNCs to the ischemic tissue using a balloon catheter, specifically ischemic myocardium in a subject in need thereof (page 1914, column 2, paragraph 2). Strauer et al. teach that said injections resulted in improved cardiac function, cardiac geometry, and contractility (page 1915, column 2).

Ueno et al. is cited as evidence that BM-MNC inherently comprises both MSCs and EPCs (paragraph 0033) and that EPCs inherently express CD34 (paragraph 0031, for example).

Yin et al. is cited as evidence that EPCs inherently express CD133, also termed AC133 (Abstract; page 5010, column 1, paragraph 3-4). Haynesworth et al. is cited as evidence that MSCs inherently express SH2, SH3, and SH4 (Abstract; Figures 1 and 2).

Claim 2 is included in this rejection because the EPCs of Ueno et al. inherently present in the BM-MNCs of Strauer et al. are considered "hemangioblasts" by virtue of their ability to form both endothelial tissue (as shown by Ueno et al.) and hematopoietic cells (as indicated by their expression of the hematopoietic marker CD34). Claims 3, 15, and 20 describe components by product-by-process limitations (*e.g.* "wherein the EPCs are generated in culture from hemangioblasts") that do not materially affect the structural or physical properties of said components; see M.P.E.P. § 2113. Claim 4 recites inherent effects of the method of claim 1.

Claim Rejections - 35 USC § 103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent

> granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-4, 6-8, 10-17, 19-21, 23-36, 40-47, 49-57, 62, and 63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ueno et al. (reference A) taken in view of Haynesworth, Yin et al., and Hess et al. (U.S. Patent 4,670,467; reference B). The claims are interpreted as being drawn to methods as described above. In some dependent claims, the EPCs are allogeneic to the recipient. In some dependent claims, the administration of cells is systemic.

The teachings of Ueno et al., Haynesworth, and Yin et al. are relied upon as above. None of Ueno et al., Haynesworth, and Yin et al. teach administering EPCs that are allogeneic to the recipient or systemic administration of the EPCs and MSCs.

Hess et al. teach that a transplant of allogeneic bone marrow can be substituted for a transplant of autologous bone marrow if the recipient is administered succinylacetone (column 4, lines 30-41, and column 6, lines 17-28).

A person of ordinary skill in the art would have had a reasonable expectation of success in substituting the allogeneic bone marrow of Hess et al. for the autologous bone marrow of Ueno et al. because Hess et al. teach specific methods for transplanting bone marrow allogeneic to the recipient. The skilled artisan would have been motivated to make said substitution for the expected benefit that the pool of bone marrow donors would be increased (Hess et al., column 1, lines 14-32).

The selection of mode of administration would have been a routine matter of optimization on the part of the artisan of ordinary skill, said artisan recognizing that Ueno et al. teach that this is an optimizable variable (paragraph 0035). A holding of obviousness over the cited claims is therefore clearly required.

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was made to substitute the allogeneic bone marrow of Hess et al. for the autologous bone marrow of Ueno et al. because Hess et al. teaches that allogeneic bone marrow is a viable substitute for an autologous transplant. It would also have been obvious to a person of ordinary skill in the art at the time the invention was made to vary the mode of administration of the cells, since Ueno et al. teach that this is an optimizable variable.

Therefore, the invention as a whole would have been *prima facie* obvious to a person of ordinary skill at the time the invention was made.

Claims 1-4, 6-8, 10-17, 19-21, 23-36, 40-47, 49-57, 62, and 63 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Kalka et al. (2000, *Proceedings of the National Academy of Sciences USA* 97: 3422-3427; reference CII on 12/3/04 IDS) or Kawamoto et al. (2001, *Circulation* 103: 634-637; reference CJJ on 12/3/04 IDS) taken in view of Pittenger et al. (2002, U.S. Patent 6,387,369; reference AW on 12/3/04 IDS), Shake et al. (2002, *Annals of Thoracic Surgery* 73: 1919-1926; reference V), Haynesworth, and Yin et al. The claims are interpreted as being drawn to a method as described above.

Kalka et al. teach isolating peripheral blood mononuclear cells (PBMCs) from human blood (page 3422, column 2, paragraph 2); sorting EPCs from said PBMCs using various antibodies, including one to CD34 (page 3423, column 1, paragraph 1); and injecting $5x10^5$ of these human EPCs into the hearts of athymic nude mice with resected femoral arteries (page 3423, column 2, paragraph 1). Kalka et al. also teach culturing and expanding the human EPCs *in vitro* (page 3424, column 2, paragraph 2) with VEGF (page 3426, column 2, paragraph 1), yielding at least an 80-fold increase in EPCs (page 3426, column 2, paragraph 2). Kalka et al. teach that mice receiving intracardiac injections of human EPCs displayed increased perfusion and neovascularization of the ischemic hindlimb compared to controls (page 3425, column 1, paragraph 2; Figure 5).

Kawamoto et al. teach isolating human PBMCs and culturing them in endothelial cell basal medium as taught by Kalka et al. (page 634, column 2, paragraph 1); and

injecting 10^6 of these human EPCs intravenously into athymic nude mice in which the coronary artery had been ligated, inducing myocardial ischemia (page 634, column 2, paragraph 2, through page 635, column 1, paragraph 1). Kawamoto et al. teach that intravenous injections of *ex vivo* expanded human EPCs preserved left ventricular function (page 636, column 2) and incorporated into foci of neovascularization (page 635, column 2, paragraph 4) of mice so treated.

Yin et al. is cited as above as evidence that EPCs express AC133/CD133.

Neither Kalka et al. nor Kawamoto et al. teach coadministering MSCs with their EPCs to treat ischemic tissue.

Pittenger et al. teach a method for regenerating or repairing cardiac muscle that has been damaged through disease or degeneration (column 1, lines 42-45) comprising isolating human MSCs from bone marrow (column 2, lines 11-13) and injecting them into the myocardial tissue of rats (Example 1; column 5, lines 30-50); Pittenger et al. teach that these MSCs incorporate into the heart tissue and become cardiomyocytes (Figures 1-3; column 6, lines 22-63; Abstract). Pittenger et al. also teach that the MSCs may be administered by any of several routes (column 4, lines 49-64) and that the MSCs may be autologous, allogeneic, or xenogeneic with respect to the recipient (column 2, lines 19-24).

Shake et al. teach isolating MSCs from the bone marrow of female swine and purifying and expanding them in culture (page 1919, column 2, paragraph 3, through page 1920, column 2, paragraph 2); inducing a myocardial infarction in swine (page 1920, column 1, paragraph 3); and injecting $6x10^7$ MSCs into the infarct region two

weeks later (page 1920, column 2, paragraph 3). Shake et al. teach the injected MSCs significantly reduced the degree of systolic dysfunction (Figure 3) and that the injected MSCs engrafted into the heart tissue (page 1922, column 2, paragraph 3). Shake et al. conclude that implanting allogeneic MSCs has "a beneficial impact on cardiac remodeling when implanted 2 weeks postinfarction" (page 1923, column 1, paragraph 2). Shake et al. speculate that injecting more cells would prolong survival in treated animals (page 1925, column 1, paragraph 4).

Haynesworth is cited as above as evidence that MSCs express SH2, SH3, and SH4.

A person of ordinary skill in the art would have had a reasonable expectation of success in combining the EPC administration of Kalka et al. or Kawamoto et al. with the MSC administration of Pittenger et al. and Shake et al. because the cited prior art teaches that both types of cells may be administered to ischemic tissues and/or patients. The skilled artisan would have been motivated to make such a combination in order to treat ischemia more effectively.

The selection of administration method would have been a routine matter of optimization on the part of the artisan of ordinary skill, said artisan recognizing that at least Pittenger et al. teach that this is an optimizable variable. A holding of obviousness over the cited claims is therefore clearly required.

The selection of the relationship between the cells and the recipient (*e.g.* autologous vs. allogeneic) would also have been a routine matter of optimization on the part of the artisan of ordinary skill, said artisan recognizing that at least Pittenger et al.

teach that this is an optimizable variable. A holding of obviousness over the cited claims is therefore clearly required.

The selection of the number of cells administered would also have been a routine matter of optimization on the part of the artisan of ordinary skill, said artisan recognizing that the cited references teach administering a variety of different numbers of cells, and that at least Shake et al. suggest administering more cells to improve the outcome of the treatment. A holding of obviousness over the cited claims is therefore clearly required.

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was made to combing the EPCs of Kalka et al. or Kawamoto et al. with the MSC administration of Pittenger et al. and Shake et al. because it is well established that duplicating components with similar functions within a composition is obvious; see *In re Harza*, 274 F.2d 669, 124 USPQ 378 (CCPA 1960) and M.P.E.P. § 2144.04. In this case, duplicating components (EPCs and MSCs) with similar functions (induction of angiogenesis) within a composition administered to a patient is obvious. It would have been further obvious to said person at the time of the instant invention to modify the selection of administration method, relationship between the cells and the recipient, and the number of each type of cell to optimize the method, because as discussed above, the cited prior art teaches that such modification comprises routine optimization.

Therefore, the invention as a whole would have been *prima facie* obvious to a person of ordinary skill at the time the invention was made.

Relevant Prior Art

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Chiu et al. (2002, U.S. Patent Application Publication 2002/0197240; reference C) teach transplanting MSCs in myocardium to grow new muscle fibers. Li et al. (2001, *Neurology* 56: 1666-1672; reference W) and Zhao et al. (2002, *Experimental Neurology* 174: 11-20; reference X) teach treating stroke in rats by administering human or rat MSCs thereto.

Conclusion

No claims are allowed. No claims are free of the art.

Applicant should specifically point out the support for any amendments made to the disclosure in response to this Office action, including the claims (MPEP 714.02 and 2163.06). Due to the procedure outlined in MPEP § 2163.06 for interpreting claims, it is noted that other art may be applicable under 35 U.S.C. § 102 or 35 U.S.C. § 103(a) once the aforementioned issue(s) is/are addressed.

Applicant is requested to provide a list of all copending U.S. applications that set forth similar subject matter to the present claims. A copy of such copending claims is requested in response to this Office action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lora E. Barnhart whose telephone number is 571-272-1928. The examiner can normally be reached on Monday-Friday, 8:00am - 4:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Wityshyn can be reached on 571-272-0926. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Lora E Barnhart

leb

SANDRA E. SAUCIER
PRIMARY EXAMINER